PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

St. Louis, Missouri

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited in the United States Postal Service as first class mail in an envelope addressed to: BOX FEE AMENDMENT, Assistant Commissioner for Patents, P.O. Box 2327, Arlington, VA 22202 on December 17, 2001.

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In re application of: :
Milbrant and Baloh :
Serial No.: 09/473,551 : Examiner Olga N. Chernyshev
Filed: December 28, 1999 : Group Art Unit 1646
For: GFR(alpha)1-RET SPECIFIC AGONISTS :
AND METHODS THEREFOR :

BOX FEE AMENDMENT
Assistant Commissioner for Patents
P.O. Box 2327
Arlington, VA 22202

EXHIBIT B

Alignment of mouse, rat and human persephins according to parameters set out in specification of U.S. Application No. 09/473,551

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                          1              15 16           30 31           45
mouse PSP (SEQ ID NO:2)   CRLWSLTLPVAELGL GYASEEKVIFRYCAG SCPQEARTQHSLVLA
rat   PSP (SEQ ID NO:3)   CRLWSLTLPVAELGL GYASEEKIIFRYCAG SCPQEVRTQHSLVLA
human PSP (SEQ ID NO:1)   CQLWSLTLSVAELGL GYASEEKVIFRYCAG SCPRGARTQHGLALA

                          46             60 61           75 76           90
mouse PSP (SEQ ID NO:2)   RLRGRGRAHGRPCCQ PTSYADVTFLDDQHH WQQLPQLSAAACGC 89
rat   PSP (SEQ ID NO:3)   RLRGQGRAHGRPCCQ PTSYADVTFLDDHHH WQQLPQLSAAACGC 89
human PSP (SEQ ID NO:1)   RLQGQGRAHGGPCCR PTRYTDVAFLDDRHR WQRLPQLSAAACGC 89
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

St. Louis, Missouri
December 10, 2001

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited in the United States Postal Service as first class mail in an envelope addressed to: BOX Petition to Commissioner, Assistant Commissioner for Patents, P.O. Box 2327, Arlington, VA 22202 on December 17, 2001.

Joseph E. Zahner
Reg. No. 48,224

In re application of:
Milbrandt and Baloh

Serial No.: 09/473,551 — Examiner Chernyshev

Filed: December 28, 1999 — Group Art Unit 1646

For: GFR(alpha)1-RET SPECIFIC AGONISTS AND METHODS THEREFOR

BOX Petition to Commissioner
Assistant Commissioner for Patents
P.O. Box 2327
Arlington, VA 22202

DECLARATION UNDER 37 C.F.R. 1.144 & 1.181

I, JEFFREY D. MILBRANDT, M.D., Ph.D., declare and state as follows:

1. I am an inventor on the U.S. Patent Application No. 09/473,551, entitled "GFRa1-RET Specific Agonists and Methods Therefor", as well as numerous other patent grants and applications relating to the GDNF family of neurotrophic growth factors and their receptors.

2. I am presently Professor of Pathology and Immunology and Internal Medicine at Washington University School of Medicine in St. Louis, Missouri, U.S.A. I am also actively involved in the Developmental Biology, Molecular Genetics, and Neurosciences Graduate Programs. My laboratory studies the biological function of neurturin, persephin, artemin and GDNF, closely related neurotrophic factors that promote survival of multiple neuronal populations including dopaminergic neurons, which degenerate in Parkinson's disease, and motor neurons, which are affected in Lou Gehrig's disease. These factors signal through a receptor complex comprised of the Ret tyrosine kinase and members of a family of GPI-linked co-receptors termed GFRα receptors. We are continuing to investigate the role of these factors and their cognate receptors in the development and function of the nervous system.

3. I received an M.D. in 1978 from Washington University and a Ph.D. in Biochemistry in 1983 from the University of Virginia.

4. I am the author or co-author of more than 126 research articles related to developmental cell biology, most of which pertain to neurotrophic growth factor signaling, 28 of which are directed specifically to the GDNF-family of related neurotrophic growth factor signaling. I am also an inventor on approximately 75 U.S. and foreign patent grants and applications directed to neurotrophic growth factor signaling.

5. I have reviewed the Office Actions of paper nos. 10 an 13. I understand that the Examiner has forced us in a restriction requirement to pick only one specific sequence of the polypeptide known as persephin. We have described in detail in the present application the amino acid sequences of portions of three species of persephin, human, mouse and rat. The persephin growth factor thus described serves as a starting template for a GFRα-1-specific ligand, which is the subject of the present invention.

6. As an experienced neurobiologist and growth factor biologist with over 20 years of research experience in the field, it is my opinion that the neurobiologist or growth factor biologist of ordinary skill in the art would consider closely related mammalian homologs *of the same growth factor* to be essentially and effectively *the same growth factor*, or at the very least species within a genus. I also understand that the "rules" of biotech patent examination are loosely fashioned around the chemical arts, and therefore it is commonplace for examiners to consider proteins that do not have the exact amino acid sequence to be distinct chemical entities and therefore separate inventions. The reality of modern day growth factor biology, molecular biology, biochemistry or biophysics, is that polypeptides, which are conveniently described by their primary structure (*i.e.* amino acid sequence) for the purposes of patenting, are defined

by their three dimensional structure and biological activity, which depends on the general secondary structure and intramolecular forces determined by the overall charge and hydrophobicity distribution of the polypeptide chain. Thus, the growth factor biologist understands that small changes in the sequence of amino acids, even as much as or more than 20% difference in primary structure (amino acid sequence), can still be tolerated in a polypeptide while that polypeptide retains its proper three dimensional architecture and specific activity.

In the present case, we have presented the sequences of the human, mouse and rat species of the persephin growth factor, as exemplified as SEQ ID NO:1, SEQ ID NO:2 and SEQ ID NO:3, respectively, which serve as the framework for our GFRα-1-specific ligand. These persephins are virtually identical in amino acid sequence and have indistinguishable growth factor properties and biological activity. The amino acid sequence of the human persephin is more than 84% identical to the mouse or rat persephin, and the mouse and rat persephins are about 97% identical to each other. When considering conservative amino acid changes (*i.e.* those amino acids that share common chemical attributes and therefore have similar effects in determining the overall shape of the polypeptide), human persephin is 94% similar to mouse or rat persephin. Thus, the skilled growth factor biologist would consider human, mouse and rat persephin the same growth factor, or at the very least, species of the same growth factor genus with minor, insignificant differences in *primary* structure.

As I stated earlier, I am also an inventor on several patent applications directed to neurotrophic growth factors and their receptors, including persephin (U.S. Patents 6,232,449, 6,222,022; U.S. Patent Applications 09/474,980, 09/128,026, 09/207,100, 09/615,944, 09/220,616, 09/220,527, 09/220,637, 09/220,407, 09/220,617), neurturin, and artemin. In the persephin applications, we present the sequences of the human, rat and mouse species of persephin along with general linking claims, and we have never been restricted to a single specific persephin sequence. In fact, we have often been able to receive patent protection for growth factors that fall within a range of percentage homology to our disclosed species of growth factors. I find it disturbing that the U.S. Patent system can restrict an invention of a growth factor to a single specific sequence, even when general claims are provided and the specific sequences are fully, clearly, concisely and exactly described in the specification. I do not see how the USPTO can consider in this particular application that mouse , rat and human persephin, which have the same biological activity and structure, except for a few amino acid substitutions, to be different inventions. This is especially incomprehensible and seemingly inconsistent, given the fact that the persephin growth factor composition has not been "restricted" in any of our other applications.

7. I declare that all statements herein made by my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application.

Dated: 12/10/01

Jeffrey D. Milbrandt, M.D., Ph.D.